March 15, 2007

John Morris
Rubber and Plastic Additives Panel
The American Chemistry Council
1300 Wilson Boulevard
Arlington, VA 22209

Dear Mr. Morris:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the revised test plan and robust summaries for the Bridged Alkyl Phenols category dated July 17, 2003. EPA posted the revised submission on the ChemRTK HPV Challenge Program Web site on September 1, 2004. The submission is a partial revision of the previously submitted category for the Hindered Phenols posted January 15, 2002. I commend the ACC Rubber and Plastic Additives (RAPA) Panel for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the RAPA Panel advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact me at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Mark W. Townsend, Chief
HPV Chemicals Branch

Enclosure

cc: O. Hernandez
C. Augustyniak
J. Willis

EPA Comments on Chemical RTK HPV Challenge Submission:
Bridged Alkyl phenols Category

SUMMARY OF EPA COMMENTS

The sponsor, the Rubber and Plastic Additives (RAPA) Panel Consortium of the American Chemistry Council, submitted a revised test plan and robust summaries to EPA for the Bridged Alkyl Phenols category, dated July 10, 2003, in response to EPA's comments on its original submission for the Hindered Phenols Category that were posted on the website on December 10, 2002. EPA posted the submission on the ChemRTK HPV Challenge Web site on September 1, 2004. The Bridged Alkyl Phenols category submission is a partial revision of the previously submitted category for Hindered Phenols dated December 18, 2001 and consists of four sponsored substances: 4,4'-(1-methyl-ethylidene)bis[2-(1,1-dimethylethyl)]phenol, CAS No. 79-96-9; 4,4'-butylidenebis(6-t-butyl-m-cresol), CAS No. 85-60-9; 2,2'-methylenebis(4-methyl-6-nonyl)phenol, CAS No. 7786-17-6; and 4,4'-thiobis(6-t-butyl-m-cresol), CAS No. 96-69-5. Robust summaries for the proposed analog, 2,6-di-t-butyl-p-cresol (BHT, CAS No. 128-37-0), were also submitted.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Definition. The category definition is adequate.

2. Category Justification. The submitter's category rationale is reasonable. However, for ecological effects, the inclusion of 4,4'-thiobis(6-t-butyl-m-cresol) is inadequately supported because the compound is significantly different from the other category members.

3. Analog Justification. 2,6-Di-t-butyl-p-cresol (butylated hydroxytoluene or BHT) is an acceptable analog for human health endpoints because of its similar chemical structure features and comparable toxicity with similar target organ effects. For ecological effects data, EPA considers that BHT, although not a full-structure analog, will provide a worst-case extrapolation.

4. Physicochemical properties. The submitter needs to provide measured melting point values for CAS Nos. 79-96-9 and 7786-17-6, a vapor pressure value for CAS No. 96-69-5 at 25 °C and measured water solubility data according to OECD TG 105 for all category members for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries.

5. Environmental Fate. The submitter needs to improve the statement on hydrolysis, provide measured ready biodegradation data for CAS No. 7786-17-6, and recalculate the fugacity values after updating the physicochemical values, as indicated in item 4 above.

6. Health Effects. Adequate data for these endpoints were submitted for one category member and the analog, allowing read-across for all the category members. The submitter needs to address deficiencies in the robust summaries.

7. Ecological Effects. Submitted data on 4,4'-butylidenebis(6-t-butyl-m-cresol) are inadequate because testing was done above the water solubility limit. Data on the analog BHT will be used to characterize the category members except for 4,4'-thiobis(6-t-butyl-m-cresol)(see item 2. above). For the latter substance, fish and aquatic invertebrates toxicity endpoints are adequate. The submitter needs to clarify the units for the algal toxicity study before it can be evaluated.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA COMMENTS ON THE BRIDGED ALKYL PHENOLS CATEGORY CHALLENGE SUBMISSION

Category Definition

The submission covers four bridged alkyl phenols in which two molecules of mono- or disubstituted alkylphenols are connected by a single carbon or sulfur atom at the 4-position. The carbon bears a hydrogen, methyl or propyl group. The category definition is clear, although 4,4'-thiobis(6-t-butyl-m-cresol) is incorrectly named 4,4'-thiobis-6-(t-butyl-m-cresol) throughout the Test Plan.

Category Justification

The similarities in structure, reactivity, uses, physicochemical and environmental fate properties, and available mammalian toxicity and ecological effects information support grouping the four bridged alkyl phenols into one category. However, for ecological effects, 4,4'-thiobis(6-t-butyl-m-cresol) is significantly different from the other category members for the following reasons: (1) the bridging of the two phenolic groups is via sulfur, unlike carbon in the other category members; (2) oxidation of the sulfur could occur in air or water changing the properties and toxicity. The reported data for this chemical appear to be of the oxidized products (sulfoxide or sulfone), as they agree with the predicted values for that chemical class. Therefore, for ecological effects, no basis for its inclusion in the category is evident, and the data on this substance cannot be extrapolated to the others.

Analog Justification

2,6-Di-t-butyl-p-cresol (BHT) is an alkylphenol with a carbon substituent corresponding to the bridging atom of the sponsored category members. Although half the size of the category molecules, its functionality is similar to the sponsored substances.

For health effects, the submitter provided adequate data for all endpoints for two sponsored compounds (CAS Nos. 96-69-5 and 85-60-9) and for BHT (CAS No.128-37-0). The LD50 values for acute oral and dermal toxicity in rats were >22000 to >7940 mg/kg for all three tested compounds. All gene mutation assays and *in vivo* chromosomal aberration assays were negative for these three chemicals (only BHT showed positive results for the *in vitro* chromosomal aberration test). The repeated-dose toxicity studies for these three chemicals indicated liver as the target organ with comparable toxicity and similar no-observed-adverse-effects levels. No pathology in reproductive organs of rats was observed in the repeated-dose toxicity studies and fetal toxicity was associated only with maternally toxic doses in studies with the sponsored compound (CAS No. 96-69-5) and BHT. Considering these similarities in data, BHT is a reasonable analog for assessing human health data for the category members.

For ecological effects, although BHT is not a full-structure analog, it is in the same structural class as the category members, has significant toxicity, and is likely to be significantly more toxic than the category members, as suggested by the differences in the log Kow values (5.1 for BHT and 7.46 to 13.10 for the category members). Using BHT data to characterize the untested category members is thus reasonable for the purposes of the Challenge Program.

Test Plan

Physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility)

The submitted data for the partition coefficient endpoint are adequate for the purposes of the HPV Challenge Program.

Melting point. The submitter provided calculated melting point values for CAS Nos. 79-96-9 and 7786-17-6. The submitter needs to provide measured melting point values for these category members because calculated melting point values above 0 °C are not adequate for the purposes of the HPV Challenge Program.

Boiling point. For CAS Nos. 96-69-5 and 85-60-9 the submitter needs to replace the "NA" in Table 1 of the test plan with the decomposition temperature values cited in the test plan. Also, the submitter needs to prepare a robust summary for the boiling point data for CAS No. 85-60-9.

Vapor pressure. For CAS No. 96-69-5, the submitter needs to provide a vapor pressure54 value at 25 °C instead of at 70 °C for the purposes of the HPV Challenge Program. For CAS No. 85-60-9, the submitter needs to prepare a robust summary of the data. For CAS No. 7786-17-6, the submitter needs to correct the discrepancy between the value reported in the robust summary [.8332648 hPa at 25 °C (0.625 mm Hg)] and the one in Table 1 of the test plan (6.25×10^{-15} mm Hg).

Water solubility. The submitter reported values of <0.1 mg/L at 25 °C for CAS Nos. 96-69-5 and 85-60-9. The submitter also reported in its robust summaries values of 0 mg/L, and 0.01139 mg/L for CAS Nos. 79-96-9 and 7786-17-6 respectively, both calculated using EPIWIN. However, in Table 1 of the test plan, the submitter indicated "ND" (No data found) for water solubility for CAS Nos. 79-96-9 and 7786-17-6. Open ended values (such as less than or greater than) and calculated values above 1 µg/L are not adequate for the purposes of the HPV Challenge Program. The submitter needs to provide measured water solubility values for all four category members according to OECD TG 105.

Environmental Fate (Photodegradation, Stability in Water, Biodegradation, Fugacity)

The submitted photodegradation data are adequate for the purposes of the HPV Challenge Program.

Hydrolysis. EPA agrees with the submitter that these chemicals are not expected to undergo hydrolysis. However, the submitter needs to incorporate this information into the robust summary for each chemical. Further, the appropriate basis for this judgment is not low water solubility (test plan p. 11) but a lack of hydrolysable groups.

Biodegradation. Measured data for CAS Nos. 96-69-5 and 85-60-9 are adequate for the purposes of the HPV Challenge Program. The submitter left the robust summary for CAS No. 79-96-9 blank and provided only calculated data (using EPIWIN) for CAS No. 7786-17-6. EPA believes it is reasonable to use the data for CAS No. 85-60-9 for read-across to CAS No. 79-96-9 owing to their structural similarity. The submitter needs to indicate this in the test plan and summaries. However, a similar read-across approach for CAS No. 7786-17-6 is not appropriate because the differences in structure are too great: nonyl rather than t-butyl substituents, and a lack of substitution on the bridging carbon atom. Thus, the submitter needs to provide measured ready biodegradation data for this chemical according to OECD TG 301.

Transport and distribution (fugacity). The submitter needs to recalculate the fugacity values for these chemicals using new measured and corrected physicochemical data as discussed above. In general, the use of estimated or calculated values introduces uncertainties that become magnified in modeling applications.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

The submitter provided adequate data for all endpoints for two sponsored compounds (CAS No. 96-69-5 and 85-60-9) and for the analog BHT. Although the submitter did not propose additional testing, the test plan did not explain the strategy for using the available data to address data gaps for the untested category members. For a read-across approach, the submitted data are adequate to address these endpoints for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries, and explain the read-across strategy in a final category analysis.

Ecological Effects (fish, invertebrates, and algae)

As stated under Category Justification, EPA does not consider 4,4'-thiobis(6-t-butyl-m-cresol) as a category member for ecological effects. For this chemical, data are adequate for fish and aquatic invertebrate toxicity endpoints. However, the submitter needs to clarify the units for the algal toxicity study to permit its evaluation. In the summary for that study, the test concentration values are reported as 60, 100, 320, 560, and 1000 mg/ml (= 1 Kg/l !). Even in mg/l, these values would be orders of magnitude higher than those reported in the daphnia (0.063, 0.125, 0.25, 0.5 and 1.0 mg/l) and fish (0.04, 0.08, 0.16, 0.25, 0.40 and 0.60 mg/l) robust summaries. The submitter needs to provide confirmation, or correction if these values should be in mg/l, or some other unit, as seems likely (the 1978 Daphnia study summary also reports test concentrations in mg/ml).

For the category member 4,4'-butylidenebis(6-t-butyl-m-cresol), the submitted data are inadequate even though effects were observed in the Daphnia study at 16 mg/L, because it appears that all aquatic tests were conducted above the water solubility limit of this chemical.

For the remaining category members, available acute and chronic toxicity data on BHT can suffice to characterize the hazard for the category. Because of its log Kow of 5.1 and high toxicity values, BHT will address data gaps as a worst-case scenario for the category members The submitter may wish to conduct appropriate testing on other category members to more accurately assess their potential aquatic toxicity.

Specific Comments on the Robust Summaries

General. A common deficiency in the robust summaries was the failure to identify the test material. The following methods of identification were inadequate: (A) giving only a physical description of the material (e.g., 'white powder' for CAS Nos. 96-69-5 and 85-60-9), (B) using acronyms or trade names not defined in the summary or in dossier section 1.2 (TBBC or Santowhite crystals for CAS No. 96-69-5, Santowhite powder for CAS No. 85-60-9), and (C) indicating 'other TS, purity n%' (for the analog BHT).

Human Health

Acute toxicity. 4,4'-Butylidenebis(6-t-butyl-m-cresol): Omissions include: group size, length of observation period (oral), duration of exposure (dermal), body weight effects (oral), and the incidence of toxic effects by dose and sex.

2,6-Di-t-butyl-p-cresol: In two oral studies and one dermal study in rats, the following deficiencies were noted: the strain of rat, the purity of the test material and the tissues examined during gross necropsy. The robust summaries for one oral and the dermal study identified the test material as 'Rhodianox BHT AP5,' the submitter needs to define the composition or the relevance of this material to the CAS number.

Repeated-dose toxicity. 4,4'-Thiobis(6-t-butyl-m-cresol): Omissions included results for mortality and body weight effects, and effects by sex; the subchronic mouse study summary did not identify what effects occurred at the LOAEL.

4,4'-Butylidenebis(6-t-butyl-m-cresol): The summary for the 90-day study did not describe the observed hepatic and lymph node pathologies.

Genetic toxicity. 4,4'-Thiobis(6-t-butyl-m-cresol): The omissions included the positive controls and source of the metabolic activation system. In an *in vivo* chromosomal aberration assay in rats the number of metaphases examined or the positive/negative controls were not reported.

4,4'-Butylidenebis(6-t-butyl-m-cresol): Summaries omitted the following critical details: cytotoxic concentration and positive controls. In an in vivo chromosomal aberration test, the names of the positive controls, the solvent, duration of exposure, and number of cells that were analyzed need to be reported.

Reproductive toxicity. 4,4'-Thiobis(6-t-butyl-m-cresol): Histopathology of reproductive organs needs to be reported in the NTP chronic rat feeding study.

4,4'-Butylidenebis(6-t-butyl-m-cresol): A robust summary lacks reporting of histopathology of reproductive organs in the 90-day rat feeding study.

2,6-Di-t-butyl-p-cresol: Robust summaries for a study in rats and in mice did not identify the test material. In the rat study, information on histopathology of male parental organs needs to be included.

Developmental toxicity. 4,4'-Thiobis(6-t-butyl-m-cresol): The rabbit study omitted purity of test compound, endpoints examined, time of termination. It did not report the size of maternal body weight effect, which is needed to adequately determine the NOAEL/LOAEL values.

2,6-Di-t-butyl-p-cresol: A robust summary for a mouse study did not report the size of organ weight changes in high-dose dams. A summary of an assay in gavaged rats was based on an abstract and did not provide sufficient study detail.

Ecological Effects

Toxicity to aquatic plants. The submitter needs to clarify units for tested concentrations and those for reported toxicity values.

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.